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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,806	12/17/2007	Martine Elisa Verhoeyen	T3103C	8052

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1638	

NOTIFICATION DATE	DELIVERY MODE
03/26/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentgroupus@unilever.com

Office Action Summary	Application No.	Applicant(s)	
	10/566,806	VERHOEYEN ET AL.	
	Examiner	Art Unit	
	EILEEN B. O HARA	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/10/06 & 8/1/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-17 are pending in the instant application.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on July 10, 2006 and August 1, 2006 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Priority

This application filed under former 37 CFR 1.60 lacks the information claiming priority to PCT/EP04/06598.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Method of Reducing Hypertension by Administering Plants with Increased Levels of Flavonol Glycosides.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-13 provides for the use of a plant which has been modified to produce increased levels of flavonol glucosides, or an extract thereof containing flavonol glucosides, in the manufacture of a composition for use in reducing hypertension, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 12 is also indefinite because it recites "the ***genetically*** modified ***vegetable*** or ***fruit***", and there is no antecedent basis for "genetically modified", "vegetable" or "fruit" in claim 1.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-13 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 and 10-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Bovy et al, WO 99/37794, July 29, 1999, (cited in IDS filed 7/10/06).

Claims 1-7 and 10-13 are drawn to a method of using a plant that has been modified to produce increased levels of flavonol glucosides, or an extract thereof containing flavonol glucosides, in the manufacture of a composition. Although claim 1 recites the use of the composition for treating hypertension, this is not given patentable weight, since the claim is not

drawn to a method of treatment, but to that of making a composition. Dependent claims recite wherein the plant or plant extract provides a daily dosage of flavonol glucoside equivalent to from about 0.1 to about 20 mg of flavonol aglycan per kg of body weight, wherein the plant is a vegetable or a fruit, wherein the plant may be from a tomato, wherein the plant has been genetically modified by stable incorporation into the genome two or more heterologous polynucleotides each encoding a different transcription factor for flavanoid biosynthesis which may be the maize C1 transcription factor and the maize Lc transcription factor, to produce increased levels of flavonol glucoside, wherein the flavonol is a quercetin glucoside, wherein the quercetin glucoside is isoquercitrin, wherein the genetically modified vegetable or fruit is from a tomato in the form of a vegetable or fruit extract or paste or other processed form.

Claims 14-16 are also drawn to a food product comprising a plant which has been modified to produce increased levels of flavonol glucosides, or extract thereof containing flavonol glucosides, a healthy supplement comprising a plant which has been modified to produced increased levels of flavonol glucosides, or extract thereof containing flavonol glucosides, wherein the plant has been genetically modified to produce increased levels of flavonol glucosides.

Bovy et al teach a method for manipulating the production of flavonoids by manipulating gene activity in the flavonoid biosynthesis pathway by expressing two or more genes encoding transcription factors for flavonoid biosynthesis and produced tomato plants (abstract). At pages 7-17 Bovy teaches that nucleic acids encoding the maize C1 transcripton factor and the maize Lc transcription factor were transformed into tomatoes, which resulted in higher levels of quercetin, kaempferal and naringenin, and that the levels of flavonols in the flesh of the tomato is at least

2mg/kg to 30 mg/kg fresh weight. Aglycons of quercetin, kaempferol and naringenin were found in the transformed plants (pages 42-47) including isoquercitrin (quercitrn-3-glucoside, page 46). Also taught is that transformation with both Lc and C1 is essential for increasing flavonoid levels in tomatoes (pages 51-52), and that tomato fruits with increased flavonoid levels by transformation with Lc and C1 exhibit increased antioxidant activity (pages 55-56). Bovy also teaches that food products such as sauces, dressings, pastes, ketchups and soups can be made (pages 8, 27, 56-58), and that many other vegetables can be transformed to increase the production of flavonoids such as peas, broccoli, tea, strawberry cauliflower, asparagus, potato sunflowers, soybeans and rape (claims 1-24). Although Bovy does not specifically state a dosage of about 0.1 to about 20 mg of flavonol aglycon per kg of body weight, Bovy does teach the amounts of flavonols procuded by the transgenic plants, and the claims are drawn to making a composition from a plant, not to a method of treatment, making the mg/kg body weight not relevant. Therefore, Bovy anticipates the claims.

Claims 1-5, 8 and 10-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Bovy et al, WO 00/04175, January, 2000 (cited in IDS filed 7/10/06).

The claims are drawn to a method of using a plant that has been modified to produce increased levels of flavonol glucosides, or an extract thereof containing flavonol glucosides, in the manufacture of a composition. Although claim 1 recites the use of the composition for treating hypertension, this is not given patentable weight, since the claim is not drawn to a method of treatment, but to that of making a composition. Dependent claims recite wherein the plant or plant extract provides a daily dosage of flavonol glucoside equivalent to from about 0.1

to about 20 mg of flavonol aglycan per kg of body weight, wherein the plant is a vegetable or a fruit, wherein the plant may be from a tomato, wherein the plant has been genetically modified to comprise a heterologous polynucleotide encoding chalcone isomerase (CHI), to produce increased levels of flavonol glucoside, wherein the flavonol is a quercetin glucoside, wherein the quercetin glucoside is isoquercitrin, wherein the genetically modified vegetable or fruit is from a tomato in the form of a vegetable or fruit extract or paste or other processed form.

Claims 14-16 are also drawn to a food product comprising a plant which has been modified to produce increased levels of flavonol glucosides, or extract thereof containing flavonol glucosides, a healthy supplement comprising a plant which has been modified to produced increased levels of flavonol glucosides, or extract thereof containing flavonol glucosides, wherein the plant has been genetically modified to produce increased levels of flavonol glucosides.

Bovy et al teach a method for manipulating the production of flavonoids in tomatoes by expressing genes encoding chalcone isomerase (CHI), and plants produced (abstract). Bovy teaches that there is increasing evidence that flavonoids are potential health-protecting components in the human diet, and that studies suggest a direct relationship between cardioprotection and increased consumption of flavonoids, in particular flavonols of the quercetin and kaempferol type, from dietary sources such as onion, apples and tea, and the flavonoids have been reported to exhibit a wide range of biological activities such as vasodilatory activity (pages 1-2). At pages 4-5, the summary of the invention describes incorporating a transgene encoding CHI incorporated into a plant to increase the flavonoid contenct, plants produced, seeds fruit and progeny, foods such as sauces, dressings, ketchups and

soups. At page 9 of the reference, Bovy teaches that upon incorporation of a gene encoding CHI, overexpression can lead to sometimes 50-100 fold increase in the amount of flavonoids and flavonols in the fruit of the plants, such as quercetin or glycosides thereof, which may be isoquercirtrin (pages 9-10, Figure 9). Also taught is other plants transformed with CHI polynucleotide to increase the production of flavonoids such as peas, broccoli, tea, strawberry cauliflower, asparagus, potato sunflowers, soybeans and rape, among others (page 12). Example 8.2, pages 34-36, discusses the flavonoids detected from tomato plants transformed with CHI, which includes quercetin and isoquercitrinand quercetin aglycons, and table II shows the concentrations of flavonoids in transformed plants. Claims 22-28 also recite transformed plants, food products and pharmaceutical product comprising part of a transformed plant. Although Bovy does not specifically state a dosage of about 0.1 to about 20 mg of flavonol aglycon per kg of body weight, Bovy does teach the amounts of flavonols procuded by the transgenic plants, and the claims are drawn to making a composition from a plant, not to a method of treatment, making the mg/kg body weight not relevant. Therefore, Bovy anticipates the claims.

Claims 1-5 and 9-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Colliver et al, EP 1 254 960, November 6, 2002, (cited in IDS filed 7/10/06).

The claims are drawn to a method of using a plant that has been modified to produce increased levels of flavonol glucosides, or an extract thereof containing flavonol glucosides, in the manufacture of a composition. Although claim 1 recites the use of the composition for treating hypertension, this is not given patentable weight, since the claim is not drawn to a method of treatment, but to that of making a composition. Dependent claims recite wherein the

plant or plant extract provides a daily dosage of flavonol glucoside equivalent to from about 0.1 to about 20 mg of flavonol aglycan per kg of body weight, wherein the plant is a vegetable or a fruit, wherein the plant may be from a tomato, wherein the plant has been genetically modified to express chalcone synthase and flavanol synthase simultaneously to produce increased levels of flavonol glucoside, wherein the flavonol is a quercetin glucoside, wherein the quercetin glucoside is isoquercitrin, wherein the genetically modified vegetable or fruit is from a tomato in the form of a vegetable or fruit extract or paste or other processed form.

Claims 14-16 are also drawn to a food product comprising a plant which has been modified to produce increased levels of flavonol glucosides, or extract thereof containing flavonol glucosides, a healthy supplement comprising a plant which has been modified to produced increased levels of flavonol glucosides, or extract thereof containing flavonol glucosides, wherein the plant has been genetically modified to produce increased levels of flavonol glucosides.

Collier et al teach a method for increasing the content of flavonoids in plants by expressing genes encoding chalcone synthase and flavonol synthase, and plants produced (abstract). Collier et al teaches that there is increasing evidence that flavonoids are potential health-protecting components in the human diet, and that studies suggest a direct relationship between cardioprotection and increased consumption of flavonoids, , from dietary sources such as plant foods, and the flavonoids have been reported to exhibit a wide range of biological activities such as vasodilatory activity (page 2). At pages 4-6, the brief description of the invention describes that the over-expression of a gene combination comprising genes encoding chalcone synthase and flavonol synthase provides plants producing increased levels of flavonoids, which may be in

the leaf or fruit tissue. At page 5 is taught that over-expression of chalcone isomerase or flavonone-3-hydroxylase can further increase the levels of flavonoids. Also taught at page 5 is that various plants can be transformed such as peas, cabbage, spinach pepper, cauliflower, apple, sunflower and tea, and that the combination of the increase of chalcone synthase and flavonol synthase results in increased querecetin. Food products are also disclosed at pages 5-6. At tables 5-7, pages 21-25, the amounts of increased flavanols from various transformed plants are show, which inclued quercetin and isoquercitrin. Although Colliver et al does not specifically state a dosage of about 0.1 to about 20 mg of flavonol aglycon per kg of body weight, Bovy does teach the amounts of flavonols procuded by the transgenic plants, and the claims are drawn to making a composition from a plant, not to a method of treatment, making the mg/kg body weight not relevant. Therefore, Colliver anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Duarte et al, British Journal of Pharmacology, Vol. 133, pages 117-124, 2001, (cited in IDS filed 8/1/06), and further in view of Bovy et al, WO 99/37794, July 29, 1999, (cited in IDS filed 7/10/06), or Bovy et al, WO 00/04175, (cited in IDS filed 7/10/06) or Colliver et al, EP 1 254 960, November 6, 2002, (cited in IDS filed 7/10/06).

Claim 17 is drawn to a method of treatment of hypertension in a mammal which method comprises administering to the mammal an effective amount of a plant which has been modified to produce increased levels of flavonol glucosides, or an extract thereof containing flavonol glucosides.

The teachings of WO 99/37794, WO 00/04175 and EP 1 254 960 are discussed above. The three references do not teach using the plants or extracts of the plants that have been modified to produce increased levels of flavonol glucosides.

Duarte et al demonstrate that administering the flavonoid quercetin to spontaneously hypertensive rats (SHR), an animal model of hypertension, resulted in reduced blood pressure

and heart rate, the cardiac renal hypertorphy, the endothelial dysfunction and the oxidant status in the SHR. Durate et al do not teach the source of the quercetin.

WO 99/37794, WO 00/04175 and EP 1 254 960 teach genetically modifying plants such as tomato in order to produce increased levels of flavonol glucosides, and foods and extracts from the plants. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to treat hypertension by administering the flavonol quercetin, as taught by Duarte et al, either by feeding plants modified to produce higher levels of quercetin, or by feeding extracts from those plants, since the plants would have higher levels and less plant material would be needed to administer the dose taught, or less extract would be needed to administer the dose taught. The motivation to use the plants or extracts from the modified plants comes from extracting more flavonol glucosides from the same amount of starting material. There would be a reasonable expectation of success, since Duarte et al demonstrates that administration of quercetin reduces hypertension, and WO 99/37794, WO 00/04175 and EP 1 254 960 demonstrate that increased levels of a number of flavonol glucosides are produced by the transformed plants. Therefore, the method is obvious in view of the teachings of the prior art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara whose telephone number is (571) 272-0878. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eileen B. O'Hara/
Primary Examiner
Art Unit 1638